Remarks

Reconsideration of this Application is respectfully requested.

Claims 24-85 are pending in the application. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Inventorship

Applicants note that a Petition Under 37 C.F.R.§ 1.48(b)(1) To Correct Inventorship in a Nonprovisional Application was filed November 6, 2000. Thus, the inventive entity is now Gregg A. Hastings, Zdenka L. Jonak, Stephen H. Trulli, James A. Fornwald, and Jonathan A. Terret.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 38-45 and 69-85 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner has maintained a previous argument from an earlier Office Action dated May 10, 2001 alleging that claims 38-45 and 69-85 are not enabled with respect to polynucleotides which are less than fully complementary to SEQ ID NOs: 1 and 125. However, this ground of rejection appears to be directed to claims 46, 47, 67, and 68 which were amended to recite "fully complementary." The Examiner indicated that claims 46, 47, 67, and 68 are allowed in the Office Action dated December 4, 2001. Thus, this ground of rejection is moot.

Claims 38-45 and 69-76

The Examiner contended that claims 38 and 69, which recited "polynucleotides at least 30 nucleotide in length" include polynucleotides that encompass much larger probes. Claims 39-45 depend from claim 38 and claims 70-76 depend from claim 69. Applicants respectfully traverse this grounds of rejection.

The Examiner stated that "[c]laims 38 and 69 have been amended to recite polynucleotides at least 30 nucleotides in length in order to direct the hybridization claims to read on probes for the disclosed sequences. However, this language still reads on much larger probes, such as cosmids, that could hybridize to the disclosed SEQ ID NO." Paper No. 19, page 2.

The test for enablement is whether the specification teaches one of ordinary skill in the art to make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Applicants submit that the hybridization claims are clearly enabled by the specification.

One of ordinary skill in the art would be able to both make and use the polynucleotides of claims 38 and 69. The sequences of SEQ ID NOs: 1 and 125 are disclosed in the application. Methods of making polynucleotides were routine and well known in the art at the time the specification was filed. Thus, one of ordinary skill in the art would be able to make polynucleotides which hybridize to SEQ ID NO:1 or 125. Further, one of ordinary skill in the art would be able to screen polynucleotides and determine, without undue experimentation, whether a given polynucleotide falls within the scope of the claims. Finally, one of ordinary skill in the art would be able to use the

polynucleotides of claims 38 and 69 because all of the polynucleotides of the claims are useful for detecting METH1 expression.

The Examiner contended that the claims may read on cosmids which hybridize to SEQ ID NO:1 or 125. One of ordinary skill in the art would know how to use such a cosmid, for example, for detecting expression of SEQ ID NO:1 or 125. This is because a polynucleotide which hybridizes to SEQ ID NO:1 is, by definition, useful for detecting expression of SEQ ID NO:1. Additionally, methods of making cosmids are routine. One of ordinary skill would thus be able to make and use polynucleotides such as, for example, cosmids.

The Examiner has not contended that any of the polynucleotides of the claims would lack usefulness as probes for detecting SEQ ID NO:1 or 125, nor that one of ordinary skill would not be able to make and/or use the polynucleotides of the claims. The claims require that any polynucleotide falling within its scope hybridize under specific conditions to SEQ ID NO:1 or 125. Thus, *all* of the polynucleotides falling within the scope of the claims are useful to detect METH1 expression.

A single use is all that is required in order for a claimed invention to meet the enablement requirement of 35 U.S.C. § 112, first paragraph. *See Raytheon Co. v. Roper Corp.*, 220 U.S.P.Q. 592 (Fed. Cir. 1983, *cert. denied*, 469 U.S. 835 (1984). Thus, the use of the polynucleotides as probes or primers is sufficient to satisfy the enablement requirement. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 77-85

With respect to claims 77-85, the Examiner appears to be of the opinion that claims directed to polynucleotides having sequences which are at least 95% identical to the polynucleotide of SEQ ID NO: 1 are not enabled. Applicants respectfully traverse the Examiner's rejection.

Claim 77, from which claims 78-85 depend, is directed to an isolated polynucleotide comprising a nucleotide sequence at least 95% identical to SEQ ID NO:1. Applicants point out that this claim is directed to a polynucleotide, not to a polypeptide. However, the Examiner maintains a point raised in a previous Office Action dated May 10, 2001 that "the claims are clearly intended to encompass species of polynucleotides that encode proteins and peptides having neither structural nor functional identity with polynucleotides encoding METH1 and no guidance has been given as to how to use these species." (Paper No. 16, page 4).

The polynucleotides of the claims do share both structural and functional identity with SEQ ID NO:1. Specifically, all of the polynucleotides of the claims are structurally related, in that they are all 95% identical to SEQ ID NO:1. That is, the polynucleotides of the claims vary by no more than 5% from SEQ ID NO:1. Further, all of the polynucleotides of the claims share functional identity with SEQ ID NO:1, as explained below.

Applicants wish to reiterate that irrespective of whether the polynucleotides of the claims encode a METH1 polypeptide, or any polypeptide at all, the specification teaches utility of these polynucleotides as hybridization probes or polymerase chain reaction primers. See specification, page 114, lines 14-24. The polynucleotides of the claims will hybridize to the reference polynucleotide, SEQ ID NO:1, and will be useful for detecting METH1

expression in various human tissues, for instance by Northern blot analysis. Thus, Applicants have disclosed how to use all of the species of the independent claim.

Applicants note that in order to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph, only one utility need be enabled. *Raytheon v. Roper*, 724 F.2d 951,958 (Fed Cir. 1983). However, Applicants assert that claims are also enabled with respect to the utility of encoding proteins that are capable of generating METH1 specific antibodies. The specification clearly teaches antigenic regions of the protein. See the description of figure 10 at page 5, lines 17-24; Table 1 at page 6; and page 231, lines 3-26. Provided with the antigenic regions, one of ordinary skill in the art would know to minimize—or altogether avoid—making substitutions, insertions and/or deletions in the disclosed regions in order to produce a polynucleotide which encodes a protein that is capable of generating METH1-binding antibodies. Accordingly, Applicants have provided ample guidance to one of ordinary skill in the art to make and use the claimed invention.

Applicants also assert that the claims are enabled with respect to utility of encoding proteins that have METH1 anti-angiogenic activity. The Examiner stated that the specification "has not shown that polynucleotides comprising variants of SEQ ID NO: 1 or 125 are capable of functioning as that which is suggested." (Paper No. 16, page 4). Contrary to the Examiner's assertion, Applicants have, in fact, shown that variants of SEQ ID NO:1 and 125 encode polypeptides which inhibit angiogenesis. For instance, Example 4, at page 304, line 6, to page 307, line 8, shows, using two different assays, that a polypeptide comprising amino acids 549-563 of METH1 inhibits angiogenesis. The skilled artisan would know to minimize-or altogether avoid-making insertions, substitutions, or deletions

of amino acid residues within this region when attempting to produce a variant protein which retains METH1 biological activity.

The specification also clearly discloses other structural regions of the METH1 protein that are important to the activity of the protein, specifically the metalloprotease, disintegrin, and TSP-like domains (page 100, lines 25-31). Furthermore, Figures 3 and 5 of the specification provide amino acid alignments of METH1, METH2, pNPI, and the TSP-like domains of METH1, METH2, and TSP 1 and 2 (page 4, beginning line 1). Regions of identity are boxed or bolded in the figures. The skilled artisan would recognize that conserved regions between two or more proteins having similar biological activity are indicative of regions important to that biological activity. Here again, the skilled artisan would know to minimize—or altogether avoid—making insertions, substitutions, or deletions of amino acid residues within these regions when attempting to produce a variant protein which retains METH1 biological activity. Moreover, the specification teaches assays for determining whether a particular polypeptide inhibits angiogenesis (page 114, line 28 to page 115, line 17).

The Examiner further states that "protein chemistry is probably one of the most unpredictable areas of biotechnology and it cannot be anticipated that a single amino acid substitution will not alter the activity of a polypeptide." (Paper No. 16, page 4). However, aside from the specific teachings in the specification about METH1, it was known in the art that, as a general matter, proteins are functionally resilient to modification. *See, e.g.*, Bowie, J.U. *et al.* "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science* 247:1206-1210 (1990). Bowie *et al.* teach that the "message [for encoding proteins] is highly degenerate in that many different sequences can code for

proteins with essentially the same structure and activity"; and that "proteins are surprisingly tolerant of amino acid substitutions." *Id.* at 1206. An exemplary protein supporting this proposition is the beta subunit of hemoglobin. It is well-known in the art that the majority of amino acid substitutions within the beta subunit of hemoglobin are functionally "silent." *See, e.g.,* Hutt *et al. Hemoglobin* 20(4):371-6 (1996) ("Approximately 700 hemoglobin variants have been reported, causing a variety of clinical manifestations, with the majority being clinically silent."). *See also* Arous *et al., FEBS Lett.* 147 (2):247-50 (1982); Ramachandran *et al., Hemoglobin* 16(4):259-66 (1992). Thus, contrary to the suggestion made by the Examiner, Applicants assert that, in general, proteins are resilient to modification and retain functional activity notwithstanding numerous amino acid substitutions, deletions and/or insertions.

In view of the overall functionally resiliency of proteins to changes in their amino acid sequence and given the fact that structurally and functionally significant regions of METH1 have been disclosed in the specification, it would not require undue experimentation for one of ordinary skill in the art to make and/or use polynucleotides which are 95% identical to SEQ ID NO:1. These polynucleotides have utility as probes or primers, utility in generating METH1-binding antibodies and utility in generating polypeptides which inhibit angiogenesis. Thus, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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